

Epidemiological Study of Non-Melanoma Skin Cancers Qazvin Province, Iran

Akram Beheshtiroy¹; Fatemeh Hajmanoochehri^{2,*}

¹Department of Dermatology, Bouali Hospital, Qazvin University of Medical Sciences, Qazvin, IR Iran

²Department of Pathology, Bouali Hospital, Qazvin University of Medical Sciences, Qazvin, IR Iran

*Corresponding author: Fatemeh Hajmanoochehri, Department of Pathology, Bouali Hospital, Qazvin University of Medical Sciences, Qazvin, IR Iran. Tel/Fax: +98-2833348217, E-mail: f.manoochehri@yahoo.com

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Background: Non-melanoma skin cancers (NMSC) are the most common cancers worldwide. These cancers are not accompanied by high mortality however they lead to various complications. Evaluation of NMSC predisposing factors could result in preventive measures, improvement of quality of life and reduction of medical costs.

Objectives: This study aimed to determine predisposing factors of non-melanoma skin cancers in the province of Qazvin (Iran).

Materials and Methods: A total of 484 proven cases of NMSC were evaluated for demographic characteristics, clinical findings, pathological type, location of lesion, and the existence of known or possible predisposing factors such as skin type, exposure to sunlight, and family and drug history within a ten-year period from 2001 to 2011. Data were recorded in a questionnaire through interview and clinical examination of patients by a physician and a dermatologist, respectively. Data were analyzed using the SPSS version 16 software and statistical tests including t-test and chi-square tests.

Results: Of the 484 patients, 294 (60.7%) were male and 190 (39.3%) were female. Most cases of carcinoma were found in basal cells (77.7%) and the rest of squamous cells. The most common sites of involvement were the head and scalp. The most frequent predisposing factors were working in the open air (70.7%), history of previous radiation for treatment of tenia capitis (26.1%), and chronic skin diseases such as burn eschar, chronic lesion, fistula and actinic keratosis (35.7%). The most prevalent Fitzpatrick skin phenotypes were II or III (75.4%). There were significant correlations between the incidence of NMSC and hookah smoking and oral contraceptive pill (OCP) consumption.

Conclusions: Skin phenotypes II and III were the most common types found in the present study and this could be due to the higher frequency of these phenotypes among the study population. The lower incidence of NMSC in areas other than the neck and scalp could be associated with the importance of covering style used by the population under study. Known risk factors for the incidence of NMSC were also observed in the present study. A history of radiotherapy for treatment of tenia capitis was observed in a considerable percentage of patients, which could lead to the incidence of cancer several decades later. Further studies are needed to determine the role of hookah smoking and the use of OCP in the occurrence of NMSC.

Keywords: Skin Cancers; Predisposing Factors; Radiation

1. Background

Skin cancer is the most common type of cancer in Iran and according to the latest report, the number of affected people is on rise and 7000 new cases are detected every year (1). The most frequent type of skin cancers is the non-melanoma skin cancer (NMSC), composing 95% of skin cancers. Non-melanoma cancers are often divided into two major classes known as squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Fortunately, these two types of cancers are slightly invasive and only produce local destruction and rarely extend to muscles, cartilage, and bones. One of the most important factors in the occurrence of skin cancers is exposure to sunlight which is extremely dangerous for all types of skin cancers, whether melanoma or non-melanoma. Another factor is the application of ultraviolet light in treating several types of skin diseases. In general, individuals who are frequently exposed to sunlight due to job situations, those

with a history of radiotherapy for a particular medical condition during childhood or adolescence, and those exposed to UV rays as one of the cosmetic techniques for tanning are considerably at risk of skin cancers. Sadly, the spread of cancerous cells in cancers associated with UV radiation emission or the development chronic lesions are more than those produced by solar radiation. However, if the skin cancer is diagnosed on time, it could be successfully treated. Therefore, timely diagnosis of skin cancers is of prime importance and repeated examinations combined with removal of predisposing factors could reduce the prevalence of these malignancies.

2. Objectives

Considering non-melanoma skin cancers, which in Iran including the province of Qazvin, rank as the first leading cause of cancers in men and the second in women

(2, 3), the present retrospective study was designed and included all patients affected by this type of skin cancer, who were referred to the dermatology clinic of Qazvin University of Medical Sciences.

3. Materials and Methods

The present study was a descriptive, analytical, cross-sectional investigation carried out on all patients referred to surgery and dermatology centers of Qazvin University of Medical Sciences within a ten-year period, from 2001-2011. The inclusion criterion to enter the study was a confirmed pathologic diagnosis of NMSC and the exclusion criterion was insufficient medical records or lack of patient's willingness to be included in the study. Data were collected through three separate questionnaires which were completed according to the patient's medical history (including the pathology report, admission file or a brief report of patient's file), patient's personal information (consisting of the place of residence, occupation, and so on), and the results of clinical examinations (including height, weight, location of the lesion, presence of underlying disease, and so forth). Data collection during 2008-2011 was conducted in the presence of patients while for the earlier years the necessary information was obtained through hospital pathology reports and also by asking the patients to attend the dermatology clinic. Information belonging to patients who were not alive at the time of study was obtained from their relatives. To determine the site of lesion, the World Health Organization International Classification of Disease for Oncology (WHO-ICD-O) system was used. In addition, the Fitzpatrick skin type classification was used to determine the skin phenotype. The sampling method used was based on an enumeration approach and data were analyzed by the SPSS version 16 software and statistical tests including t-test and chi-square test.

4. Results

During the period of study, a total of 1793 cases of skin biopsies were performed of which one-third was associated with NMSC with 484 cases available for follow-up and therefore were entered in the study. Of the 484 patients, 294 (60.7%) cases were male and 190 (39.3%) females. The minimum age of patients was 13 years and the maximum 110, both with BCC. The overall mean age was 62.9 ± 16.1 years (63.4 ± 15.42 years for BCC patients and 62.5 ± 16.79 for SCC patients). Most patients were in their sixth or higher decades of life (58%). The lowest age frequency was associated with the second decade of life (3.7%). Among men, 219 cases (74.5%) had BCC and 75 (25.5%) had SCC and in women the figures for BCC and SCC were 157 cases (82.6%) and 33 cases (17.4%), respectively. There was a significant correlation between the occurrence of NMSC and sex, with higher prevalence of both types of tumors in men ($P = 0.03$). Clinically, the diagnosis of malignancies in 452 cases (93%) was in agreement with pathology reports. Re-

garding education level, most cases were people with an education level lower than high school certificate (74.1%) and a significant correlation between lower education level and the occurrence of tumor was found. Considering professional activity, 231 cases (47.7%) were farmers and herders, 131 cases (27%) housekeepers, and 65 cases (13.4%) labors and in 70.7% of cases the job was carried out in an open work environment. Furthermore, regarding the place of residence for the first ten years of life, 167 cases (34.5%) lived in the city (Qazvin) and 317 cases (65.5%) in villages, while 249 cases (51.4%) and 235 (48.6%) were living in the city (Qazvin) and villages in the last ten years of life, respectively. Among villagers, BCC was observed in 175 cases (74.5%) and SCC in 60 cases (25.5%) with no significant correlation between the place of residence in the first and the last ten years of life and NMSC. Table 1 shows the site of tumor involvement with nose as the most common place for the occurrence of tumor.

Underlying genetic skin diseases were found in 16 patients (3.3%) including two cases of xeroderma pigmentosum, 11 cases of albinism, and three cases of epidermolysis bullosa. A history of chronic inflammatory skin disease was observed in 173 patients including burn scars (33 cases), chronic ulcers (23 cases), trauma and fractures (9 cases) and chronic osteomyelitis (seven cases), while sunburns and actinic keratosis (35 cases) were the most important types of chronic inflammatory skin diseases. The rest of the patients had a history of chronic skin disease including psoriasis (14 cases), acnes and hirsutism (61 cases) and lupus (8 cases), while some patients were found to be affected by more than one such medical condition. From the total of 484 patients, 12 cases (2.4%) had a history of NMSC among first-degree relatives. Clinical diagnosis and treatment of lesion were performed at different time intervals, where 238 patients were diagnosed and treated in less than one year, 201 cases between one and five years, 38 between five and ten years, and seven patients ten years after the incidence of lesion. Among the medications consumed by the patients, the oral contraceptive pill (OCP) was the only important drug used. A history of OCP use was found in 102 women (21.1%) in whom a significant correlation between OCP consumption and NMSC was found ($P = 0.04$). The most frequent time of exposure to sunlight was between 11.00 AM and 3.00 PM, observed in 348 cases and there was a significant correlation between the peak hours of sunlight and the occurrence of NMSC ($P < 0.01$). In total, 68 cases had skin type I, 144 had type II, 221 had type III and 51 had type IV, with no statistical correlation between the four different skin phenotypes and the existence of NMSC ($P = 0.8$). Cigarette smoking was found in 245 cases (50.6%), hookah smoking in 249 cases (51.4%), and 138 cases (28.5%) were opium smokers or addicted to other narcotics. While no significant correlation between cigarette smoking and NMSC was established, a significant correlation between hookah smoking and NMSC was observed ($P = 0.02$). A history of radiotherapy was found in 143 cases (29.4%),

of whom 127 cases (26.1% of total patients) were associated with treatment of tenia capitis during the previous decades. A history of different types of cancers was revealed in 27 patients (5.5%) including melanoma (two cases), lymphoma (three cases), breast cancer (five cases), colorectal cancer (six cases), lung cancer (two cases), prostate cancer (three cases), stomach cancer (four cases), esophageal cancer (one case), and liver cancer (one case). Overall, 381 cases (78.7%) returned to normal and cancer-free conditions following treatment; 45 cases (9.3%) died from causes other than NMSC and 58 cases (12%) stayed alive but with complication at the site of lesion.

Table 1. Tumor Involvement Sites ^a

Site	Cases
Auricle, Periorbital, Perioral Areas	124 (25.7)
Neck and Scalp	94 (19.4)
Nose	141 (29.1)
Cheeks	30 (6.2)
Forehead	34 (7)
Trunk and Waist	13 (2.7)
Upper extremity	19 (3.9)
Lower extremity	29 (6)
Total	484 (100)

^a Data are presented as No. (%)

5. Discussion

Non-melanoma skin cancers are common at older ages however there are rare reports on the occurrence of NMSC in children in whom a genetic background and underlying disease are often blamed. The most common age for contracting the disease among our patients was during the sixth decade of life. The findings of the present study over age and sex frequencies were consistent with those of others (4, 5). Our study showed that the NMSC are more common in men rather than in women. This finding is also in agreement with the results of a report published by the Iranian Cancer Registry Office in which a higher prevalence of NMSC in men, compared to women, was documented (2). Likewise, in a study by Radespiel et al. conducted between 2001-2005 in Germany, a higher prevalence of NMSC was observed in men compared with women (6). The role of solar light as an influential factor in developing NMSC is fully accepted. Our study showed that the most affected people were farmers and herders who were repeatedly exposed to sunlight for long periods of time. Previous studies also highlight the role of long-term exposure to sunlight on people who work outdoors or perform physical exercises in open environments, which predispose these individuals to NMSC (5, 7, 8). Radespiel et al. in a report from Germany in 2009 described that outdoor jobs and contact with sunlight are mostly accompanied by BCC, a finding in harmony

with the results of the present study (6). Similarly, in another study by Vishvakarman and Wong an association between outdoor job and skin cancer was demonstrated (9). The ratio of developing BCC to SCC was 3.1 in our study which is compatible with those of others. In studies carried out between 1999 and 2005 at the Babol (Iran) Cancer Registry Station (affiliated to the School of Public Health, Tehran University of Medical Sciences), a similar ratio (3.1) was found (10). The distribution of malignancy in different parts of the body was similar to the findings of other studies in which the head and neck were described as the most common sites for developing cancer however, the involvement of other regions was less frequent compared to findings of similar studies from other countries and this could be associated with the type of clothing used by men and women in Iran which protect people against the development of skin cancer in other areas of the body (5). In the present study, unlike studies carried out in European countries (9, 11, 12), the light skinned phenotype (fair skin phenotype) was not the dominant skin type of our patients. This could be related to the low number of light skin phenotype (fair skin phenotype) in the study population. Therefore, it could be concluded that in regions where the light skin phenotype is not the leading skin type, the significance of this phenotype in developing cancer becomes less important. Regarding the underlying skin diseases, genetic skin diseases were observed in a small percentage (3.3%) of patients in the present study. This, in addition to highlighting the role of genetic diseases in developing cancer, also indicates that these diseases are rare and therefore environmental factors, which are preventable, compose a higher percentage of predisposing factors. The role of genetics, in particular skin and hair color in developing non-melanoma cancers is well established (13, 14). In our study, although a significant correlation between the use of OCPs and NMSC was found, yet recognizing whether this issue is purely an accidental finding or a real risk factor needs further in-depth investigations. Estrogen could facilitate the pathway towards development of tumor through amplifying epidermal growth factor (EGF) signaling, estrogen-induced expression of proto-oncogene, and inhibition of apoptosis (15). It is generally accepted that OCP consumption contributes to skin cancer (16). In a cohort study by Birch-Johansen et al. on 29875 patients in Denmark between 1993-1997, it was demonstrated that the role of hormone replacement therapy (HRT) in developing NMSC is greater than OCP (17). The role of UV radiation from artificial sources, unlike studies carried out in other countries, was not considered as a predisposing factor (18) because of limited availability of equipment and also unpopularity of UV tanning beds or UV tanning salons among members of the Iranian population. In contrast, a considerable proportion of our patients had a history of radiation therapy in particular for the treatment of tenia capitis. Application of X-ray for treating "tenia capitis was a commonly used procedure between

1930 and 1950; although the routinely used X-ray dose was low (100-500 rad) but the follow-up of these patients within decades later showed that a considerable portion of these patients were affected by NMSC in the areas of head and neck. The minimum time course between exposure to radiation and the development of cancer has been reported to be 30 years. In our study, 21.6% of patients had a history of exposure to X-ray for treating alopecia and the minimum duration between exposure to radiation and development of cancer was 50 years. It was reported that 200000 children were treated by this therapeutic protocol in the United States between 1930 and 1950 and further follow-ups were indicative of at least a fourfold rise in the prevalence of NMSC in these people, compared to other unexposed members of the public, and that the prevalence of BCC in these individuals was higher than SCC (19). Previous studies have shown that patients with chronic radio dermatitis characterized by atrophy of the skin, skin pigmentation disorders, and xerosis are more susceptible to cancer development; a finding consistent with the data found in the present study (15). In our study, the place of residence during the first ten years of life was in villages for most cases (65.2%); however, this figure decreased to 48.4% within the most recent decade, demonstrating a heavy migration from villages to cities. Since farming and animal husbandry were the most common professions (47.6%) among our patients, it could be concluded that the overall frequency of disease is higher among villagers and therefore necessary education concerning preventive measures against the incidence of these cancers must be part of village-based programs that focus on this target group. The correlation between NMSC and nutrition, use of immunosuppressive drugs, and skin diseases such as seborrheic keratosis, sunburn and chronic ulcers is a matter of controversy. Our study found that 35.6% of patients had underlying skin diseases. Considering the role of various predisposing factors in the occurrence of NMSC, changes in lifestyle including sunlight avoidance, use of appropriate clothing, proper nutrition, and education can play a crucial role in preventing the development of NMSC in susceptible individuals.

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Authors' Contributions

Akram Beheshtiroy: study design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content and study supervision. Fatemeh Hajmanoochehri:

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References

1. Inanlou H. *An introduction to medical geography of skin cancer in Iran; statistical classification based on the National Cancer Report*. Iran: Iran Ministry Health Med Educ; 2010.
2. *A report by the National Cancer Registry*. Iran: Department of Health Center for Disease Control and Prevention, Iran Ministry Health Med Educ; 2006.
3. *Evaluating the status of cancers in the province of Qazvin during 2006-2010*. Iran: Qazvin University of Medical Sciences, Department of Health Education and Health Promotion Executive Committee; 2011.
4. Lotfinezhad S, Rashidi T, Eshghi MJ. The frequency of malignant skin tumors in patients referred to health centers of Oroumeh (Iran). *J Ardebil Univ Medical Sci*. 2003.
5. Vishvakarman D, Wong JC, Boreham BW. Annual occupational exposure to ultraviolet radiation in central Queensland. *Health Phys*. 2001;**81**(5):536-44.
6. Radespiel-Troger M, Meyer M, Pfahlerberg A, Lausen B, Uter W, Gefeller O. Outdoor work and skin cancer incidence: a registry-based study in Bavaria. *Int Arch Occup Environ Health*. 2009;**82**(3):357-63.
7. Moehrle M. Outdoor sports and skin cancer. *Clin Dermatol*. 2008;**26**(1):12-5.
8. Downs N, Parisi A, Schouten P. Basal and squamous cell carcinoma risks for golfers: an assessment of the influence of tee time for latitudes in the Northern and Southern hemispheres. *J Photochem Photobiol B*. 2011;**105**(1):98-105.
9. Vishvakarman D, Wong JC. Description of the use of a risk estimation model to assess the increased risk of non-melanoma skin cancer among outdoor workers in Central Queensland, Australia. *Photodermatol Photoimmunol Photomed*. 2003;**19**(2):81-8.
10. *A report on non-melanoma skin cancers in northern region of Iran during 1998-2009*. Tehran, Iran: Babol Research Station School of Public Health University of Tehran; 2010.
11. Suarez-Varela MM, Llopis Gonzalez A, Ferrer Caraco E. Non-melanoma skin cancer: a case-control study on risk factors and protective measures. *J Environ Pathol Toxicol Oncol*. 1996;**15**(2-4):255-61.
12. Han J, Qureshi AA, Nan H, Zhang J, Song Y, Guo Q, et al. A germline variant in the interferon regulatory factor 4 gene as a novel skin cancer risk locus. *Cancer Res*. 2011;**71**(5):1533-9.
13. Kwasniak LA, Garcia-Zuazaga J. Basal cell carcinoma: evidence-based medicine and review of treatment modalities. *Int J Dermatol*. 2011;**50**(6):645-58.
14. Ramachandran S, Rajaratnam R, Smith AG, Lear JT, Strange RC. Patients with both basal and squamous cell carcinomas are at a lower risk of further basal cell carcinomas than patients with only a basal cell carcinoma. *J Am Acad Dermatol*. 2009;**61**(2):247-51.
15. Leslie KK, Espey E. Oral contraceptives and skin cancer: is there a link? *Am J Clin Dermatol*. 2005;**6**(6):349-55.
16. Quinn AG, Perkins W. Non-Melanoma Skin Cancer and Other Epidermal Skin Tumours. In: Burns T, Breathnach S, Cox N, Griffiths C editors. *Rook's textbook of dermatology*. New Jersey Hoboken: Wiley Blackwell; 2010.
17. Birch-Johansen F, Jensen A, Olesen AB, Christensen J, Tjonneland A, Kjaer SK. Does hormone replacement therapy and use of oral contraceptives increase the risk of non-melanoma skin cancer? *Cancer Causes Control*. 2012;**23**(2):379-88.
18. Wehner MR, Shive ML, Chren MM, Han J, Qureshi AA, Linos E. Indoor tanning and non-melanoma skin cancer: systematic review and meta-analysis. *BMJ*. 2012;**345**.
19. Ronel DN, Schwager RG, Avram MR. Squamous cell carcinoma of the scalp after radiotherapy for tinea capitis. *Dermatol Surg*. 2004;**30**(3):446-9.